Investigating the contribution of genetic risk variants to Attention Deficit/Hyperactivity Disorder trajectories in the general population

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Abstract

Importance. Attention Deficit Hyperactivity Disorder (ADHD) is a highly heritable neurodevelopmental disorder that shows clinical and genetic overlap with other childhood neurodevelopmental problems. ADHD symptom levels typically decline across childhood/adolescence, although remain elevated for some individuals. The determinants of symptom persistence and decline are not yet fully understood.

Objective. Test the hypothesis that genetic risk variant load for ADHD (indexed by polygenic risk scores (PRS)), but not for other psychiatric disorders, is associated with population-based ADHD symptom trajectories across childhood/adolescence. As a secondary objective, examine whether higher ADHD genetic liability is correlated with childhood multi-morbidity (total number of additional neurodevelopmental problems).

Design, setting and participants. A prospective population-based cohort design, The Avon Longitudinal Study of Parents and Children (ALSPAC): ongoing data collection since 1990. 14,701 children were alive at 1 year, 9575 individuals with data on ADHD symptoms at multiple time-points were included.

Main Outcome and Measure(s). ADHD symptom trajectories from ages 4 to 17 years (7 time-points). The primary exposure variables, PRS, were generated in ALSPAC using genome-wide association study results from the Psychiatric Genomics Consortium. Childhood multi-morbidity scores (age 7-9 years) were measured by total impairments (0-4) in four domains known to share genetic liability with ADHD: (i) IQ, (ii) Social-communication, (iii) Pragmatic language, and (iv) Conduct.

Results. Four ADHD symptom trajectories were identified: low (82.6%), intermediate (7.7%), childhood-limited (5.8%) and persistent (3.9%). ADHD PRS were higher in

the persistent compared to each of the other 3 trajectories ($\chi^2(1)$=4.70-14.67, *p*<0.001-0.03, OR=1.22-1.31). Findings were specific to ADHD PRS; other psychiatric PRS did not differ across trajectories. Multi-morbidity was also highest in the persistent trajectory ($\chi^2(1)$= 31.16-136.85, *p*<0.001, OR=1.90-6.83) and was associated with persistence independent of PRS.

Conclusions and Relevance. ADHD symptom persistence across childhood/adolescence in the general population is associated with higher ADHD PRS. Childhood multi-morbidity was also associated with persistence and may help to identify children with ADHD whose symptoms are most likely to continue into adolescence.

Keywords: ALSPAC; ADHD; trajectories; polygenic risk scores; genetic; multimorbidity; longitudinal

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Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that has its onset in childhood.[1-3] Although considered to manifest most commonly in children, around 15% of people with a childhood diagnosis continue to meet clinical criteria for ADHD in adult life, with up to 65% showing sub-threshold ADHD.[4] Furthermore, recent work suggests that for some individuals, ADHD emerges newly in adult life,[5-7] highlighting the need to investigate the natural history of ADHD in general population samples. While ADHD is relevant across the lifespan, most children show a decline in symptom levels across childhood/ adolescence - a feature of other childhood-onset neurodevelopmental disorders such as autism spectrum disorder, communication and specific learning disorders.[1] The determinants of neurodevelopmental disorder persistence are not fully understood, although for ADHD, initial symptom severity, comorbidities, cortical maturation and familial loading among other factors have been considered as contributors.[8-15]

ADHD is highly heritable with a heritability estimate of 71-90%.[16] Twin studies suggest that ADHD symptom persistence is also highly heritable, but it has only recently become possible to directly assess genetic contributions.[8,17-19] Genomic studies of ADHD have revealed a genetic architecture of multiple common risk alleles as well as rare mutations.[16] Although individual common risk alleles typically have small effect sizes for multifactorial disorders like ADHD, composite measures - polygenic risk scores (PRS) - representing an individual's estimated total burden of common risk alleles (where risk alleles are defined by their association statistics and effect sizes in a discovery GWAS) have been found to be useful biological indicators of disease risk.[19] ADHD PRS are higher in patients with disorder than controls[21] and are associated with ADHD symptom levels in the general population.[22,23] ADHD also shares genetic liability with other neurodevelopmental traits and conduct

problems,[1,21,24] suggesting that those with higher ADHD genetic loading are likely to manifest elevated levels in these domains.

We set out to examine the relationships between psychiatric PRS and population-based developmental trajectories of ADHD symptoms from early childhood to adolescence. We hypothesized that PRS for ADHD, but not for other psychiatric disorders (schizophrenia, bipolar disorder, depression) would be associated with ADHD symptom persistence from ages 4 to 17 years. We also postulated that a trajectory of persistent ADHD symptoms would be associated with a higher burden of childhood neurodevelopmental impairments and conduct problems, as this "multi-morbidity" would index underlying ADHD genetic liability.

Method

Sample

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a well-established prospective, longitudinal birth cohort study. The enrolled core sample consisted of 14,541 mothers living in Avon, England, who had expected delivery dates of between 1st April 1991 and 31st December 1992. Of these pregnancies 13,988 children were alive at 1 year. When the oldest children were approximately 7 years of age, the initial sample was increased by recruiting eligible families who had failed to join the study originally, resulting in an additional 713 children being enrolled. The resulting total sample size of children who were alive at 1 year was N=14,701. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. All participants provided written informed consent. Full details of the study, measures and sample can be

found elsewhere[25,26] (see http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary). Where families included multiple births, we included the oldest sibling. Individuals were included in our analyses where primary data on ADHD symptoms (see below) were available for at least two time-points: N=9575. The numbers of individuals with data at different time-points are given in the Supplementary Materials.

ADHD symptoms

The primary outcome was ADHD symptoms assessed repeatedly across time using the parent-rated 5-item Strengths and Difficulties Questionnaire (SDQ)[27] subscale designed to measure hyperactive-inattentive symptoms (range 0-10). In-line with recommendations and to maintain consistency with previous work in ALSPAC,[27,28] abnormal scores were defined as those ≥7 and borderline scores as those=6. The SDQ showed high sensitivity/specificity for detecting a DSM-IV diagnosis of ADHD assessed using a diagnostic interview at age 7 years (see Supplementary Materials). Data were available from parent reports at ages 47, 81, 97, 115, 140, 157 and 198 months: roughly age 4 to 17 years.

Polygenic risk scores

PRS were generated as the standardized mean number of disorder risk alleles in approximate linkage equilibrium (R^2<0.25), weighted by GWAS allele effect size (see below), derived from dosage data of imputed autosomal SNPs using standard procedures.[20] Risk alleles were defined as those associated with case-status in the Psychiatric Genomics Consortium (PGC) analyses of several phenotypes at a threshold of p<0.5 for ADHD, bipolar disorder and depression and p<0.05 for

schizophrenia (these thresholds maximally capture phenotypic variance[29-34]) (GWAS case/control sample sizes: ADHD 5,621/13,589; schizophrenia 35,476/46,839; bipolar disorder 7,481/9,250; depression 9,240/9,519 respectively). Genotyping and full PRS details are given in the supplementary materials. Power was estimated using the Dudbridge calculator with approximations for some of the required parameters.[35]

Other characteristics

We investigated whether the burden of co-occurring neurodevelopmental and conduct problems in childhood (at age 7-9 years) are associated with ADHD genetic liability (defined by PRS). Problems (defined categorically using established cut-points to enable computation of "multi-morbidity") included: (i) *Low IQ* - Wechsler Intelligence Scale for Children IQ <80.[36] (ii) *Social-communication problems* - parent-rated Social and Communication Disorders Checklist ≥9.[37] (iii) *Pragmatic language impairment* - parent-rated Children's Communication Checklist subscale ≤132.[38] (iv) *Conduct problems* - parent-rated SDQ subscale ≥4 (91 months).[27] *Multi-morbidity was* defined as the sum of the number of impairments in domains i-iv (range 0-4).

Statistical analysis

Latent class growth analysis (LCGA) was conducted in Mplus[39] to identify ADHD developmental trajectories across all 7 time-points, using binary ADHD symptom data, in-line with previous work in ALSPAC.[28] LCGA aims to group individuals into categories ("classes") based on different patterns of change (growth curves) across multiple time-points, with within-class covariance matrices fixed to zero (i.e. individuals within the same class are specified to have the same growth curve).[40]

Starting with a single *k*-class solution, *k*+1 solutions are fitted until the optimum solution is reached. Models were run using a robust maximum likelihood parameter estimator and full information maximum likelihood (FIML) estimation.[39] The optimal number of categories was determined using adjusted Bayesian information criterion (BIC) to assess model fit and entropy to assess classification accuracy. Differences in PRS and multi-morbidity were assessed by a Wald test of equality of means using posterior probability based multiple imputations (ORs were generated using multinomial logistic regressions),[41] which takes profile measurement error into account (PRS and multi-morbidity were not used to generate the trajectories). Finally we investigated the independent associations of ADHD PRS and multi-morbidity with class membership using a bias-free three-step approach (R3STEP)[42] that performs better than conventional 3-step methods.[43]

Results

ADHD symptom trajectories

LCGA indicated the 4-class solution of ADHD trajectories to have the best model fit (adjusted BIC=25574.45; Vuong-Lo-Mendell-Rubin likelihood ratio test $p<0.001$ compared to a 3-class solution) and classification accuracy (entropy=0.82), consistent with previous work in ALPSAC.[28] As shown in Figure 1, this included the 4 classes: low (82.6%), intermediate (7.7%), childhood-limited (5.8%) and persistent (3.9%). The solution did not include an adolescent-onset group. The proportion of males differed across the trajectories, with the largest proportion in the persistent (72.9%), smallest in the low (48.0%) and intermediate levels in the child-limited and intermediate trajectories (62.3% and 63.0% respectively) (overall $\chi^2(3)=45.22$, $p<0.001$).

Genetic variables: psychiatric polygenic risk scores

As shown in Table 1, ADHD polygenic risk scores differed across the four trajectories; scores were highest in the persistent trajectory, lowest for the low symptom group and intermediate for the other two classes. Differences were observed for the persistent trajectory when compared separately to the childhood-limited group (χ^2=6.50, *p*=0.01, OR=1.26), intermediate (χ^2=4.70, *p*=0.03, OR=1.22) and the low trajectory class (χ^2=14.67, *p*<0.001, OR=1.31). The association with trajectory was specific to the ADHD PRS: PRS for schizophrenia, bipolar disorder and depression were not associated with ADHD symptom trajectories (see Table 1).

Childhood multi-morbidity

The proportion of individuals with neurodevelopmental and conduct problems across the 4 trajectories are shown in Table 2. Low IQ, social-communication problems, pragmatic language impairment and conduct problems at ages 7-9 years all differed by class (χ^2(3)=12.76-103.50, *p*<0.001-0.005), with highest levels in the persistent class compared to all other classes (χ^2(1)=6.73-225.86, *p*<0.001-0.009). The childhood-limited and intermediate trajectories also showed elevated levels compared to the low class.

The proportions of individuals with multi-morbidities across the 4 trajectories are shown in Table 2. Multi-morbidity varied by latent class trajectory (more than 1 neurodevelopmental/conduct domain affected χ^2(3)=38.93, *p*<0.001; more than 2 domains χ^2(3)=17.31, *p*=0.001) with a higher burden of childhood impairments/problems in the persistent class compared to all other classes (total

multi-morbidity $\chi^2(1)=31.16\text{-}136.85$, $p<0.001$, OR=1.90-6.83) and elevated levels in the childhood-limited and intermediate compared to the low class.

Independent contributions of ADHD PRS and childhood multi-morbidity to ADHD persistence

Multi-morbidity at age 7-9 years was associated with ADHD PRS (OR=1.16, $p<0.001$) but not with PRS for schizophrenia, bipolar disorder or depression (OR=1.02-1.09, $p>0.05$).

Persistent vs. low class. When entered simultaneously (N=3688), both multi-morbidity and ADHD PRS were independently associated with persistent class membership compared to the low class (multi-morbidity B=2.22, SE=0.15, $p<0.001$, OR per additional neurodevelopmental/conduct domain= 9.21; PRS B=0.35, SE=0.13, $p=0.01$, OR per standard deviation increase in ADHD PRS = 1.42)..

Persistent vs. childhood-limited class. There was also evidence that multi-morbidity was independently associated with ADHD persistence relative to the childhood-limited class (B=0.38, SE=0.14, $p=0.01$, OR per additional neurodevelopmental/conduct domain= 1.46), whereas evidence for ADHD PRS was weak (B=0.26, SE=0.18, $p=0.14$, OR per standard deviation increase in ADHD PRS = 1.30).

Grouping individuals using ADHD cut-points at two time-points

Given recent findings on "adolescent-onset" ADHD,[5-7] in a *post-hoc* investigation we categorized individuals as showing ADHD symptom persistence if they scored above

the SDQ ADHD subscale cut-point at two time-points: ages 7 and 17 years (N=4824; individuals with data on ADHD symptoms at both time-points).

Most individuals did not meet the threshold for high levels of ADHD symptoms at either age and were categorized as *low* (N=4193, 86.9%). Around 10% of individuals (N=481) met the cut-point at age 7; the majority of these no longer met the cut-point at age 17 and were categorized as *child-limited* (N=370, 7.7%), with those meeting the cut-point at both ages categorized as *persistent* (N=106, 2.2%). Around three percent (N=155) did not meet the threshold for high levels of ADHD symptoms at ages 7, but did at age 17 years (.3% had borderline levels of ADHD traits at age 7 years).[27] We categorised an *adolescent-onset* subgroup as those who met the abnormal cut-point at age 17 but did not have borderline or abnormal symptoms at age 7: (N=122; 2.5% of the total sample).

As shown in Table 3, ADHD PRS differed across the four ADHD groups (F(3,3644)=3.01, *p*=0.03) but PRS for schizophrenia, bipolar disorder and depression did not (F(3,3644)=0.66-2.01, *p*=0.11-0.58). Specifically, there was evidence of higher ADHD PRS in the persistent compared to the low subgroup (B=0.29, SE=0.11, *p*=0.01, OR per standard deviation increase in ADHD PRS = 1.34), as shown in Figure 2. Follow-up analyses categorizing individuals using (i) age 4 and 17 year symptoms, (ii) age 12 and 17 year symptoms, (iii) inattentive and hyperactive/impulsive traits separately - all revealed the same pattern of results (shown in Supplementary Materials).

Discussion

This study aimed to test the hypothesis that ADHD common risk allele burden as indexed by polygenic risk scores (PRS) contributes to population-based ADHD developmental trajectories from early childhood to adolescence. Defining susceptibility alleles for a range of psychiatric disorders from large patient case-control discovery samples,[29-34] we found that in a population-cohort, higher ADHD PRS were associated with persistence of ADHD symptoms but that other psychiatric genetic risk scores were not. The persistent trajectory also had the highest burden of multi-morbidity for neurodevelopmental and conduct problems in childhood.

While ADHD typically onsets - and is thought to be most common - in childhood, around 15% of children with a childhood diagnosis show persistence across childhood and adolescence and still meet diagnostic criteria for ADHD in adulthood[4] while only around 35% achieve full remission.[2,4] In-line with this, and previous work in the ALSPAC population cohort,[28] we identified two trajectory groups of individuals with a high probability of having initially elevated ADHD symptoms in childhood (total 9.7%). Of these, around 40% were estimated to be in the persistent trajectory, with a high probability of elevated ADHD traits at age 17 years old. The other 60% were estimated to be in a childhood-limited trajectory, with a low probability of high ADHD traits after around age 10.

We found that ADHD genetic risk scores were higher specifically in the trajectory with persistent symptoms compared to those with consistently low symptoms and childhood-limited symptoms. Twin studies that indirectly infer genetic contributions, have suggested that most of the persistence in ADHD symptoms is explained by additive genetic variance and is highly heritable.[8,17-19] Those with persistent ADHD also have a higher familial load with almost a 4-fold higher risk of

illness in their families than individuals with childhood ADHD.[18,44] Some twin studies suggest that different genetic risk factors are associated with persistence - compared to the baseline levels - of ADHD traits.[45] Our work suggests that common genetic variants associated with ADHD diagnosis contribute to the persistence of ADHD traits in the general population, as well as initial childhood levels, found in previous work.[22,24] The finding that ADHD PRS were higher in those with persistent vs. childhood-limited symptoms is novel and potentially clinically important given that these trajectories would be indistinguishable on the basis of their ADHD symptoms in early childhood, although this would need replicating in a clinical sample.

As well as being associated with ADHD genetic risk, we also found the persistent ADHD trajectory class to be strongly associated with multi-morbidity - low IQ, social communication problems, pragmatic language impairment and conduct problems in childhood. Individual childhood co-morbidities have been implicated as possible predictors of ADHD persistence[14] but a global burden of multi-morbidity has not previously been assessed. Although highest in the persistent class, multi-morbidity was also elevated in the childhood-limited class. ADHD shares genetic liability with childhood neurodevelopmental traits and conduct problems in the general population[21,22,24] and this study shows ADHD PRS to be associated with multi-morbidity in these domains. Thus it is plausible that multi-morbidity might be an observable early phenotype marker of this loading and be associated with ADHD developmental trajectories. When controlling for multi-morbidity, ADHD PRS was no longer associated with persistence compared to childhood-limited symptoms – suggesting that the overall childhood burden of neurodevelopmental morbidity may be a phenotypic correlate, and perhaps for now a better index, of a higher genetic loading. Further work will be needed to assess the predictive value of multi-

morbidity. Although this is a population-based sample, the findings highlight the likely developmental, biological, and clinical importance of multi-morbidity, an issue that until now has been considered a healthcare problem in old age.[46,47] In clinical settings, typically we use a hierarchical approach to simplify and reduce the number of diagnoses. Assessing and describing multi-morbidity are therefore not easily achieved with current approaches, yet might be very important for clinical reasons and for scientific research.

Recent work has suggested that some forms of ADHD emerge in adult life.[5-7] Although our trajectory analyses did not identify an adolescent-onset class, using an alternative method for defining ADHD course, we identified a subgroup of around 2.5% of individuals who had elevated levels of ADHD traits at age 17 but not age 7 years. While our study focused on an earlier age, in-line with the observation made by Moffitt and colleagues, this adolescent-onset subgroup did not show elevated ADHD genetic risk scores.[5] While it is possible this is due to low PRS power, we did find an association for the persistent subgroup, despite this being smaller. This is now the fourth population study which suggests that a substantial proportion of adolescents/young adults with ADHD have onset at later ages and that finds a very low rate of ADHD persistence; moreover our study finds this pattern when using the same informant (parent) at both time-points.

Our findings should be considered in light of some limitations. ALSPAC is a longitudinal birth cohort study with non-random attrition, and more complete data are likely to have been available for individuals with lower levels of psychopathology as well as PRS.[48] However, we used FIML which fits the model to the non-missing values for each observation, allowing the use of all cases including those with

missing data.[49] Results using an alternative method examining two time-points (ages 7 and 17 years) in individuals with complete data revealed the same pattern of higher ADHD PRS for children with persistent ADHD traits. In addition, we used a questionnaire measure to investigate ADHD symptom trajectories, which may not generalize to ADHD diagnosis although the SDQ cut-point is well validated against diagnosis. Further, due to current discovery sample sizes, psychiatric PRS currently explain only a small proportion of the heritability and of phenotypic variance and are therefore underpowered (around 0.60 for the analysis using two-time-points).[35] However our intention was not to explain substantial proportions of phenotype variance, but to use PRS as a molecular index of common genetic loading. Finally, ADHD data in ALSPAC were only available up to age 17 years and future work is needed into environmental factors that may also contribute to the developmental course of ADHD.

Conclusion

We found ADHD genetic risk to be associated with the developmental course of ADHD traits from early childhood to adolescence in the general population: specifically, ADHD genetic loading was highest in individuals with persistent symptoms. Genome-wide association studies may benefit from deeper phenotyping of cases to characterize the developmental course of psychiatric disorders. ADHD persistence was also associated with a higher multi-morbidity of childhood neurodevelopmental impairments and conduct problems, which may be a phenotypic correlate of genetic loading and help to identify children with ADHD who are most likely to show persistence into adolescence.

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Author contributions.

Dr Riglin and Prof Thapar had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors

Acquisition, analysis, or interpretation of data: Riglin, Collishaw, AK. Thapar, Maughan, O'Donovan, Thapar

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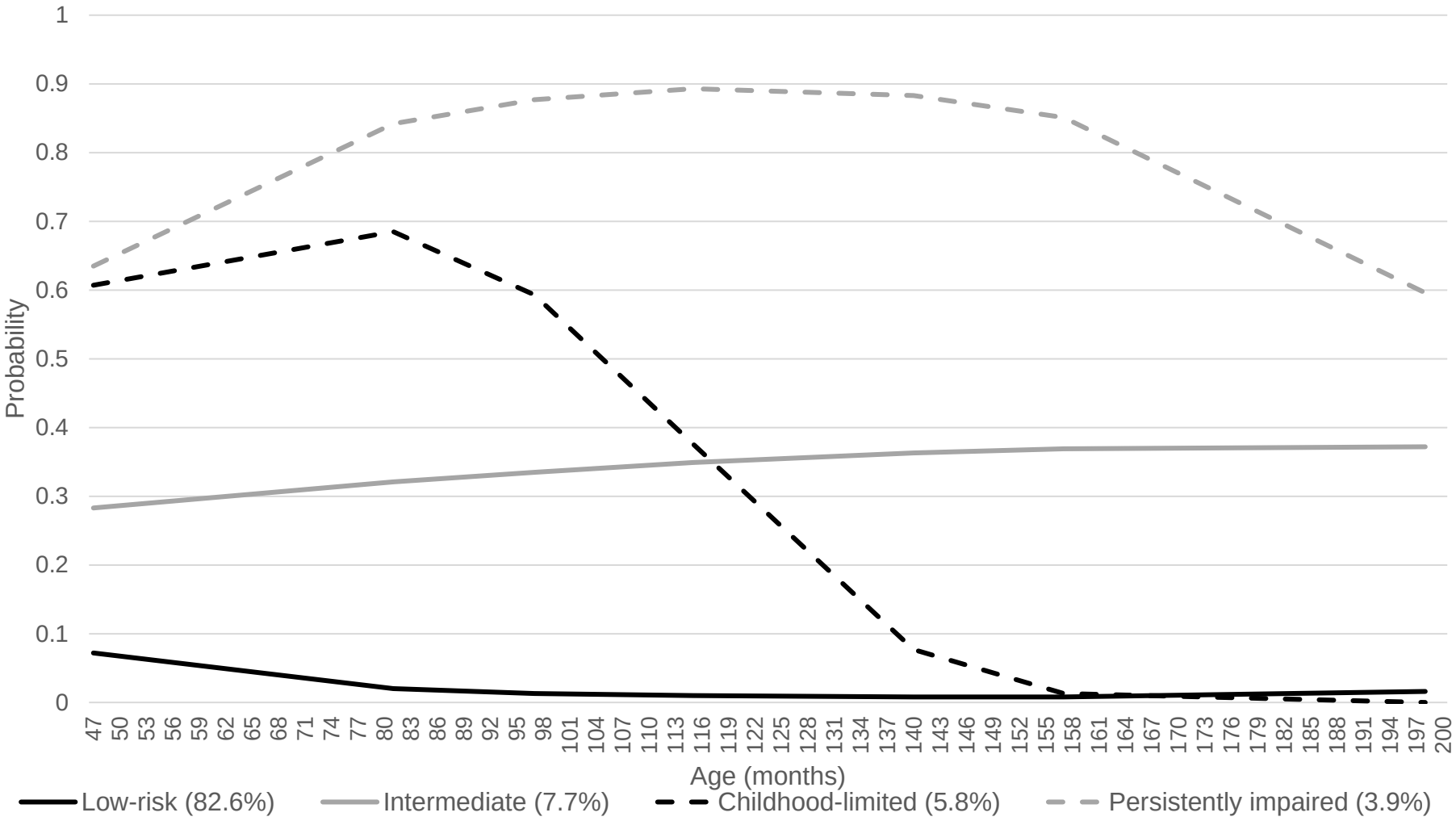
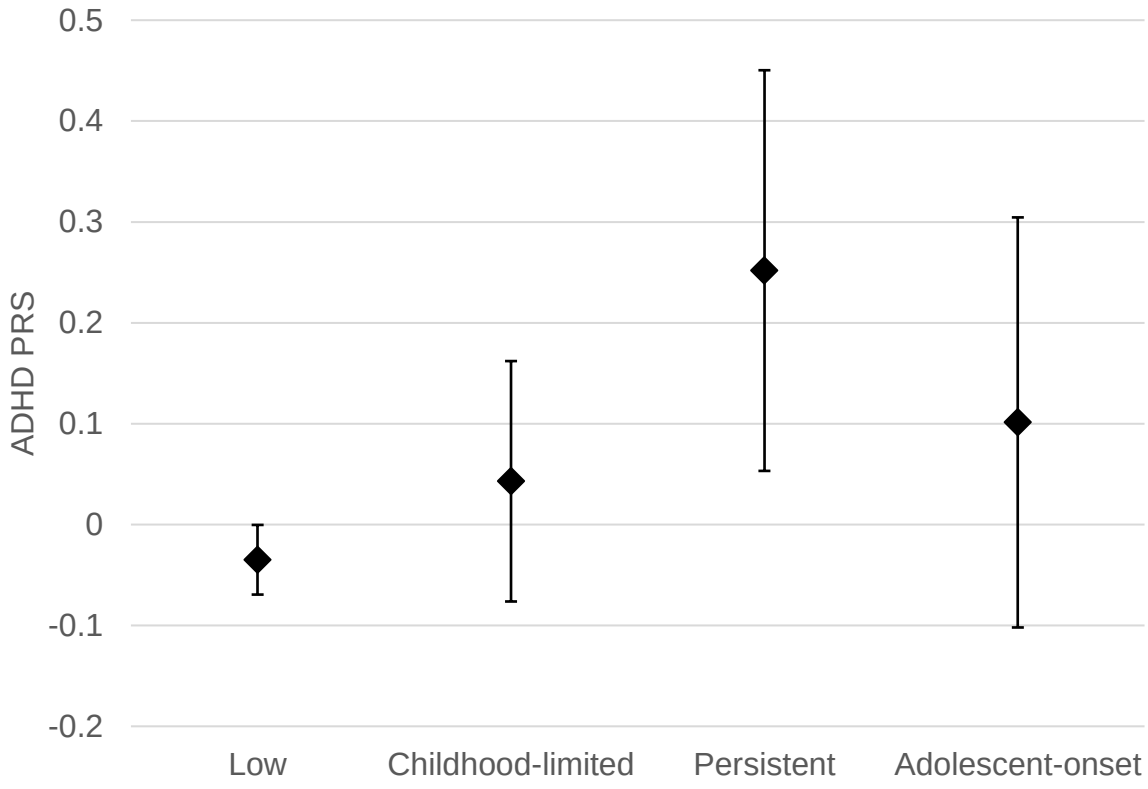


Figure 1. Probability of being in the high-scoring range for ADHD symptoms, by latent class

Figure 2. Mean ADHD polygenic risk score (PRS) by ADHD subgroup, based on two time-points (age 7 and 17 years) with 95% confidence interval error bars



Legend: ADHD = Attention Deficit Hyperactivity Disorder; PRS = polygenic risk score. ADHD Subgroups based on two time-points (age 7 and 17 years) with 95% confidence interval error bars

Table 1: Associations between psychiatric polygenic risk scores and all ADHD latent trajectory classes

	Mean (SE)				Overall test	
Polygenic risk score	Low	Intermediate	Childhood-limited	Persistent	$\chi^2(3)$	*p*
ADHD	-0.018 (.014)	0.054 (.055)	0.017 (.060)	0.254 (.069)	7.83	0.05[#]
Schizophrenia	-0.008 (.014)	0.026 (.054)	0.037 (.059)	0.064 (.072)	0.44	0.93
Bipolar disorder	-0.003 (.014)	-0.022 (.055)	0.059 (.066)	0.018 (.070)	1.15	0.77
Depression	-0.011 (.014)	0.022 (.055)	0.067 (.060)	0.092 (.071)	1.105	0.78

[#]Higher ADHD polygenic risk scores in the persistent compared to low, intermediate and childhood-limited classes ($\chi^2(1)$=4.70-14.67, p<0.001-0.030).

Table 2: Associations between co-occurring childhood characteristics at aged 7 years and ADHD trajectory class

	Proportion (95% CI)								Overall test	
	Low		Intermediate		Childhood-limited		Persistent		$\chi^2(3)$	*p*
Low IQ	5.4%	(4.8-6.0)	11.4%	(8.1-14.7)	11.7%	(7.8-15.6)	21.4%	(15.5-27.3)	12.76	0.005[#]
Social-communication problems	3.4%	(3.0-3.8)	19.9%	(16.0-23.8)	22.9%	(18.2-27.6)	53.1%	(46.6-59.6)	103.50	<0.001[#]
Pragmatic language impairment	1.2%	(1.0-1.4)	7.7%	(5.0-10.4)	10.3%	(7.0-13.6)	27.8%	(22.1-33.5)	36.51	<0.001[#]
Conduct problems	6.7%	(6.1-7.3)	21.1%	(17.0-25.2)	27.5%	(22.6-32.4)	42.0%	(35.7-48.3)	56.62	<0.001[#]
Multi-morbidity										
More than 1 additional problem	1.7%	(1.3-2.1)	13.1%	(8.6-17.6)	16.1%	(10.8-21.4)	42.5%	(33.9-51.1)	38.93	<0.001[#]
More than 2 additional problems	0.2%	(0.0-0.4)	2.8%	(0.6-5.0)	3.4%	(0.7-6.1)	17.8%	(11.3-24.3)	17.31	0.001[#]

[#]Greater proportion in the persistent compared to low, intermediate and childhood-limited classes ($\chi^2(1)$=6.73-225.86, *p*<0.001-0.009) and in the intermediate and childhood-limited compared to low class ($\chi^2(1)$=5.25-68.15, *p*=<0.001-0.02).

Table 3: Associations between psychiatric polygenic risk scores and ADHD symptoms at ages 7 and 17 years

	Mean (SE)				Overall test	
Polygenic risk score	Low	Childhood-limited	Persistent	Adolescent-onset	F(3,3644)	*p*
ADHD	-0.035 (.018)	0.043 (.061)	0.252 (.102)	0.101 (.104)	3.01	0.03[#]
Schizophrenia	-0.035 (.018)	-0.014 (.058)	0.098 (.107)	0.050 (.118)	0.66	0.58
Bipolar disorder	-0.001 (.018)	0.081 (.061)	0.117 (.120)	-0.133 (.107)	1.43	0.23
Depression	-0.017 (.018)	0.089 (.057)	0.036 (.130)	-0.196 (.108)	2.01	0.11

[*]p<0.05. [#]Higher ADHD polygenic risk scores in the persistent compared to low group (B=0.29, SE=0.11, *p*=0.01) (see Figure 2).

Supplementary materials

ALSPAC genotyped data

In total 9912 ALSPAC children were genotyped, of whom 8365 passed quality control. Of these, 6700 had ADHD symptoms data at two-time points and were therefore included in this study. Full genotyping details and individual exclusion criteria are described elsewhere.[1] Known autosomal variants were imputed with MACH 1.0.16 Markov Chain Haplotyping software[2, 3] using CEPH individuals from phase 2 of the HapMap project (HG18) as a reference set (release 22) resulting in a total N=2,543,887 SNPs. Dosage data were transformed from MACH output to PLINK format using fcGENE.[4] After quality control exclusions (call rate <95%, MAF <1%, HWE $P>5x10^{-7}$, $R^2 \geq .7$) there were 1,813,169 autosomal SNPs. EIGENSTRAT principal components analysis was used to generate the top 100 components after the removal of known regions of long linkage disequilibrium in the data.[5, 6] EIGENSTRAT analysis revealed no additional obvious population stratification and genome-wide analyses with other phenotypes indicate a low lambda. Previous work has included the top 10 EIGENSTRAT principal components analysis in secondary analyses[7]. We investigated whether these may need to be included in our analyses by testing for differences in these 10 principal components across our outcome variables: we found weak evidence of differences between the ADHD trajectories ($\chi^2(3)=0.05$-2.80, $p=0.42$-1.00) or between groupings of individuals using ADHD cut-points at two time points ($F(3,3644)=0.11$-2.50, $p=0.06$-$.96$). EIGENSTRAT principal components were therefore not included as covariates in our analyses.

Mental disorder risk alleles were identified from the Psychiatric Genetic Consortium (PGC) meta-analysis of case-control GWAS of ADHD (5,621 cases and

13,589 controls/pseudo-controls), schizophrenia (35,476 cases and 46,839 controls), bipolar disorder (7,481 cases and 9,250 controls) and depression (9,240 cases and 9,519 controls).[8-13] PGC SNPs were limited to those that passed an imputation quality control threshold akin to that set for the target sample (INFO score >=0.7).

Autosomal SNPs that were present in both the target and discovery sample were limited to those in relative linkage equilibrium using the --clump command in PLINK[12, 14] with an R^2 threshold of .25 and a distance threshold of 500kb, retaining SNPs with the lowest association p-value. In-line with previous work,[15] for schizophrenia PRS, only a single SNP within the extended major histocompatibility complex (MHC; chromosome 6: 25-34Mb) was included due to the high linkage disequilibrium (LD) within this region. This resulted in 153,652, 185,051, 149,512, and 157,210 clumped SNPs for ADHD, schizophrenia, bipolar disorder and depression respectively. These were used to generate polygenic risk scores using the --score command. Scores were calculated as the mean number of risk alleles weighted by effect size (log odds ratio). PRS were standardized using Z-score transformation for those with genetic data included in this study (N=6664).

ALSPAC ADHD symptoms measure

We used ROC curve analysis to assess the validity of the ADHD symptom subscale of the Strengths and Difficulties Questionnaire (SDQ)[16] in detecting a DSM-IV ADHD diagnosis. ADHD diagnosis was assessed using parent reports of the Development and Well-Being Assessment, a well-established research diagnostic assessment.[17] Diagnoses were generated originally using computer generated diagnoses designed to complement clinician diagnoses and for examining risk factors.[18] Children were defined as having a diagnosis if they were in the highest computer predicted band

(70% of children in this band predicted to have disorder). Using the SDQ 'abnormal' cut-point of ≥7, the area under the curve was 0.88. Of those with who had a diagnosis, around 86% reached the SDQ cut-point (sensitivity) and of those who did not have a diagnosis around 90% did not reached the SDQ cut-point (specificity); of those who reached the SDQ cut-point, 6% had a diagnosis (positive predictive value) and of those who did not reach the SDQ cut-point 99.9% did not have a diagnosis (negative predictive value), which reflect the low prevalence of ADHD diagnosis in this sample.

Additional analyses: grouping individuals using ADHD cut-points at two time-points

We grouped individuals based on parent rated Strengths and Difficulties Questionnaire[16] responses at two-ages to categorize individuals as low, childhood-limited, persistent or adolescent-onset, in-line with definitions in the main manuscript.

a) Age 4 and 17 years

Using data from age 4 and 17 years (N=4915), 83.9% of individuals were categorized as low, 10.7% childhood-limited, 1.9% persistent and 2.8% adolescent-onset (.7% excluded as they reached the cut-point at age 17 but were borderline at age 4). ADHD PRS differed across the subgroups (F(3,3677)=4.71, *p*=0.003). PRS for schizophrenia, bipolar disorder and depression did not differ by subgroup (F(3,3677)=0.43-1.05, *p*=0.37-.73). Specifically, there was evidence of higher ADHD PRS in the persistent compared to the low (B=0.34, SE=0.12, *p*=0.01). There was evidence of higher ADHD PRS in the child-hood limited compared to the low (B=0.12, SE=0.05, *p*=0.03), as shown in Figure S2a.

b) Age 12 and 17 years

Using data from age 12 and 17 years (N=4953), 90.9% of individuals were categorized as low, 3.9% childhood-limited, 2.2% persistent and 2.4% adolescent-onset (.6% excluded as they reached the cut-point at age 17 but were borderline at age 12). ADHD PRS differed across the subgroups ($F(3,3746)=7.93$, $p<0.001$). PRS for schizophrenia, bipolar disorder and depression did not differ by subgroup ($F(3,3746)=0.60$-1.00, $p=0.39$-$.62$). Specifically, there was evidence of higher ADHD PRS in the persistent compared to the low (B=0.51, SE=0.11, $p<0.001$), childhood-limited (B=0.43, SE=0.15, $p=0.004$) and adolescent-onset (B=0.70, SE=0.19, $p<0.001$) subgroups, as shown in Figure S2b.

Age 7 and 17: inattentive and hyperactive-impulsive symptoms separately

Individuals were also grouped based on parent rated Strengths and Difficulties Questionnaire[16] responses at ages 7 and 17 years separately for inattentive and hyperactive-impulsive symptoms. Inattentive scores were the summed items 'Easily distracted, concentration wanders' and 'Sees tasks through to the end' (reverse coded) (possible range 0-4). Hyperactive-inattentive scores were the summed items 'Restless, overactive', 'Constantly fidgeting or squirming' and 'Thinks things out before acting' (reverse coded) (possible range 0-6). Somewhat in-line with the cut-point for abnormal scores for the total subscale being 7/10 (70% of total possible score)[16] the cut-point for inattentive and hyperactive-impulsive symptoms were selected as 3 and 4 respectively.

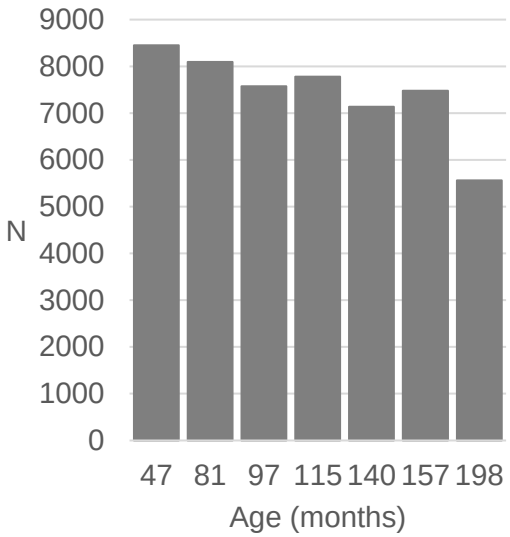
c) Inattentive symptoms

For inattentive symptoms, (N=4757), 77.2% of individuals were categorized as low, 8.3% childhood-limited, 5.6% persistent and 8.9% adolescent-onset. ADHD PRS differed across the subgroups (F(3,3623)=4.34, *p*=0.01). PRS for schizophrenia, bipolar disorder and depression did not differ by subgroup (F(3,3623)=0.18-1.92, *p*=0.12-91). Specifically, there was evidence of higher ADHD PRS in the persistent compared to the low (B=0.23, SE=0.07, *p*=0.001), as shown in Figure S2c.

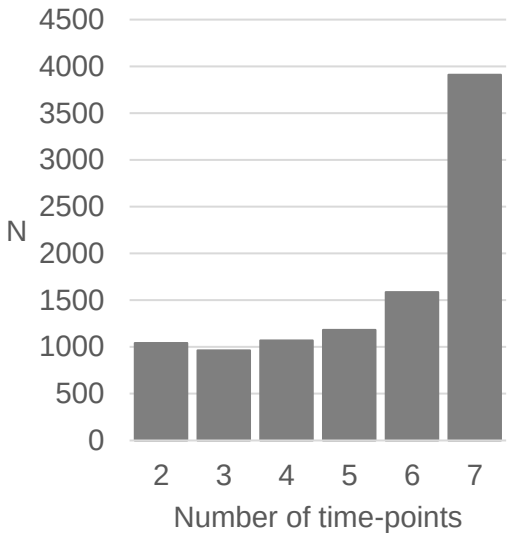
d) Hyperactive-impulsive symptoms

For hyperactive-impulsive symptoms (N=4535) 82.2% of individuals were categorized as low, 11.8% childhood-limited, 2.9% persistent and 3.2% adolescent-onset. ADHD PRS differed across the subgroups (F(3,3452)=3.06, *p*=0.03). PRS for schizophrenia, bipolar disorder and depression did not differ by subgroup (F(3,3452)=0.30-1.62, *p*=0.18-.83). Specifically, there was evidence of higher ADHD PRS in the persistent compared to the low (B=0.25, SE=0.10, *p*=0.02) subgroup, as shown in Figure S2d.

a) Individuals with ADHD symptom data at each time point



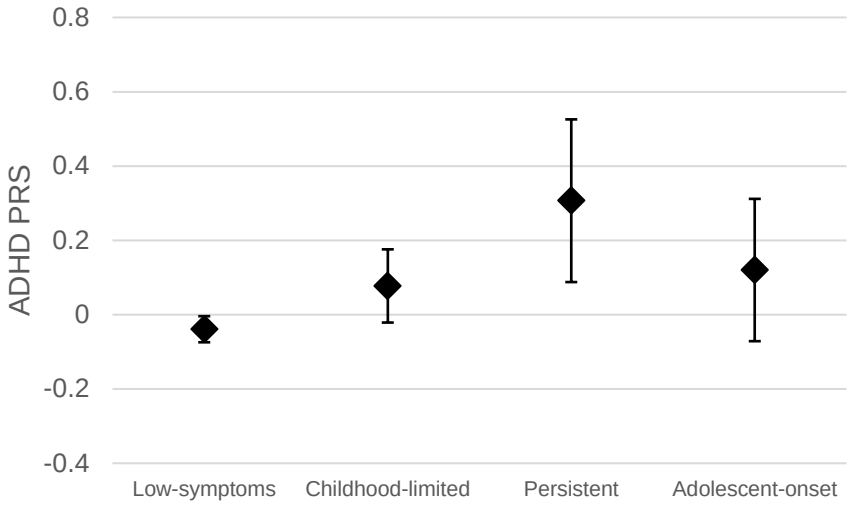
b) Number of time-points individuals had ADHD symptom data available



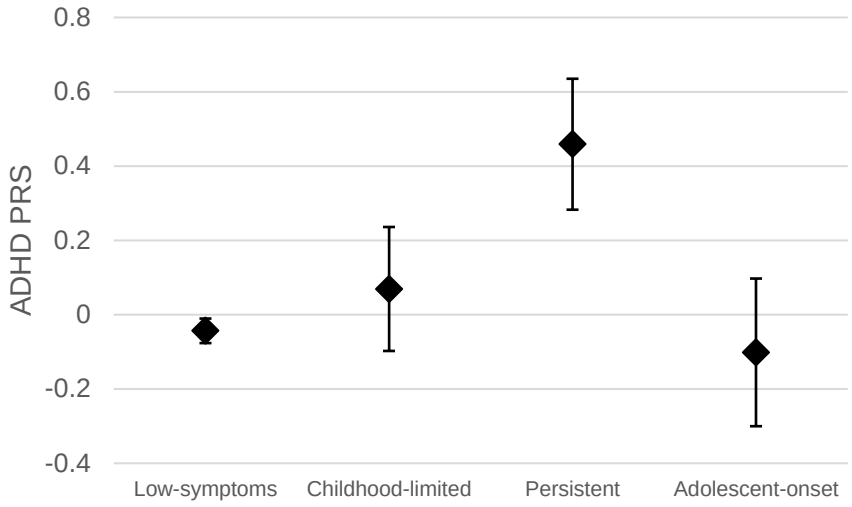
NB. Individuals with ADHD symptom data at fewer time points were less likely to be in the low class (mean number of time-points 5.38) compared to the intermediate, childhood-limited or persistent classes (mean number of time-points = 5.19, 5.14 and 4.96 respectively) ($\chi^2(1)=3.72\text{-}14.44$, $p<0.001\text{-}.054$).

Figure S1. Number of individuals with ADHD symptom data at each time point

a) Age 4 and 17 years



b) Age 12 and 17 years



c) Age 7 and 17 years: Inattentive symptoms

d) Age 7 and 17 years: Hyperactive-impulsive symptoms

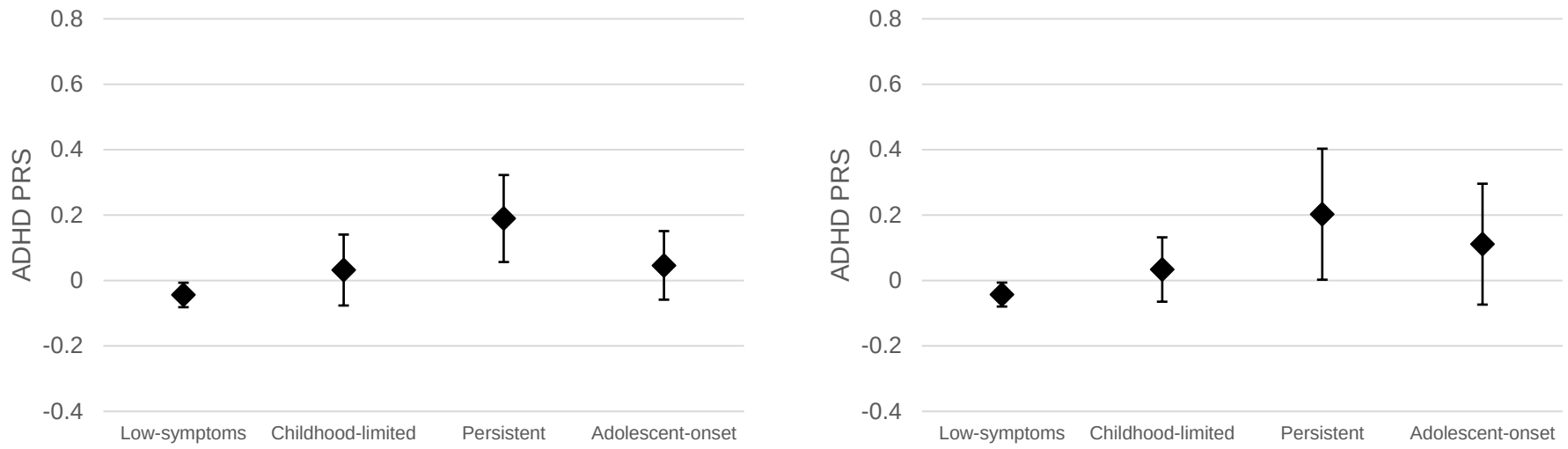


Figure S2. Mean ADHD polygenic risk score (PRS) by subgroup, based on two time-points with 95% confidence interval error bars

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